Robust pharmacokinetic analysis for population studies in Breast Cancer detection using the Mohan-Shinagawa model

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Abstract. The pharmacokinetic (PK) analysis of breast MRI data using prior methods like the Tofts model-based approaches involved the estimation of the amount of contrast agent (CA) fed to the tissue, called the Arterial Input Function (AIF). The Mohan-Shinagawa model (henceforth referred to as the M-S model), is a novel expanded model (derived from the Tofts model) proposed in (1). It analytically eliminated the AIF from the analysis but required the robust selection of suitable reference regions across images. In this paper, the authors propose a novel framework for Tofts model estimation, using the M-S model as an intermediate stage. The advantages are that the AIF estimation is eliminated, and the final estimated PK parameters are independent of the reference region selected. This highly simplifies the overall analysis and improves the robustness in population studies by reducing the bias introduced by the reference region selection while keeping the advantages of the M-S framework including a reduction in scattered false positives. Also, as compared to the M-S model, the physical interpretation of the Tofts model parameters is well documented (2). This framework could potentially also be used for analysing DCE-MRI of other anatomical structures.

1 Introduction

The diagnosis of breast cancer from Magnetic Resonance Imaging (MRI) data is a difficult problem exacerbated by the fact that a malignant lesion often displays intensity patterns similar to benign tissues and other structures (such as the vessels) in the field of view. However, malignant tissues differ from benign tissues in how Contrast Agents (CA) flow in and leak out. The CA molecules affect the observed intensity patterns because they change the longitudinal relaxation times at the voxels in the image. Malignant tissues display a characteristic pattern with regard to the amount of CA that washes in, and the rates of entry and washout of the CA. Dynamic Contrast-Enhanced (DCE) MRI uses this kinetic property to identify regions of interest. PK analysis aims to quantify this washin and washout of the CA towards differentiating malignant and benign lesions. PK analysis aims to provide a framework where the kinetics of CA within the tissue of interest can be quantitatively described and compared across data sets

from one or more patients and/or MR systems. However, many current systems do not meet this requirement due to the limited normalization that the system can perform on the input image data, which impairs the effectiveness of any population studies conducted.
Existing models for Pharmacokinetic analysis for breast MR can be categorized into two broad classes - compartmental and heuristic (3; 4; 5). The first class describes the microscopic view of the breast tissues as a set of compartments and models the interaction between these compartments with respect to the entry and exit of the CA. Heuristic models try to model the washin and washout phenomena - as growing(/decaying) exponentials for example - and quantify these characteristics. Of the compartmental models, the Tofts model (2) is the most commonly used. The M-S model (1) was derived as an attempt to address the issues in the Tofts model with respect to the normalization over data sets, and the estimation of the Arterial Input Function (AIF). The approach was the use of a reference region (RR) concept previously explored in work such as (6) with the RR as the nipple region (detected by using the work in (7)). While this RR approach performed well on the population study performed in (1), it possessed the disadvantage that the RR selection affected the extent of normalization. This affected its reliablity in population studies. This paper proposes a framework based on the M-S model which addresses the sensitivity to RR while keeping the original advantages of the model. The approach is to estimate the Tofts model parameters from the M-S model parameters. Since this decorrelates the voxel-wise Tofts model parameters, the framework is in theory independent of the choice of RR as verified by the results in this paper. At the same time, by the initial estimation of the M-S model parameters, we retain the advantage of not needing to estimate or approximate the AIF.

2 The M-S model

2.1 Model

The M-S model describes the concentration of Contrast Agent (CA) at a voxel under analysis, with respect to that at a reference voxel. The model is given by:

$$c_T(t) = (A_1 e^{-B_1 t} + A_2 e^{-B_2 t}) * c_R(t) + A_3 c_R(t) \tag{1}$$

Here, $c_T(t)$ denotes the concentration at the voxel being analysed, and $c_R(t)$ denotes the concentration at the reference voxel. A_1, B_1, A_2, B_2 and A_3 denote the parameters of the M-S model which are functions of the Tofts model parameters at the two voxels being considered.
To recapitulate the extended Tofts model, the time-behavior of the concentration of CA at the voxel under analysis and the reference voxel are described as:

$$c_T(t) = v_p c_p(t) + K^{trans} c_p(t) * e^{-k_{ep} t} \tag{2}$$

$$c_R(t) = v_p^R c_p(t) + K^{trans^R} c_p(t) * e^{-k_{ep}^R t} \tag{3}$$

where $c_p(t)$ denotes the true AIF, v_p, K^{trans} and k_{ep} are the Tofts model parameters for the voxel being analysed, and v_p^R, K^{trans^R} and k_{ep}^R are the Tofts model parameters for the reference voxel. A more detailed explanation can be found in (2).

From (1), the M-S model parameters are related to the Tofts model parameters at the two voxels as follows:

$$
\begin{aligned}
A_1 &= \frac{{K^{trans}}^R}{v_p^R(k_{ep}-k_{ep}^R)-{K^{trans}}^R}\frac{v_p(k_{ep}^R v_p^R+{K^{trans}}^R)-v_p^R(k_{ep}v_p+K^{trans})}{{v_p^R}^2} \\
A_2 &= \frac{(k_{ep}^R-k_{ep})K^{trans}}{v_p^R(k_{ep}^R-k_{ep})+{K^{trans}}^R} \text{ and } A_3=\frac{v_p}{v_p^R} \\
B_1 &= k_{ep}^R+\frac{{K^{trans}}^R}{v_p^R} \text{ and } B_2=k_{ep}
\end{aligned}
\tag{4}
$$

2.2 Advantages of the M-S model over Tofts model-based approaches with standard AIF

Existing pharmacokinetic frameworks that use the extended Tofts model require the AIF for analysis, and since it is difficult to measure AIF in vivo, it has to be estimated in a reasonable fashion for the subsequent analysis to be reliable. The work in (1) has demonstrated that Tofts model estimation with the standard AIF yields results that are not satisfactory for population studies with the use of one standard AIF for all subjects reducing the extent of normalization of the results across patients.

The M-S model (1) utilized the fact that the AIF is by definition the concentration of the CA being fed to the tissue under analysis, and used the concept of a reference region to relate the concentration of the CA at the voxel under analysis to that of the reference voxel rather than the AIF. This eliminated the AIF from the analysis. This further led to the advantage that with the reference region being selected uniformly across data sets from different subjects, the estimated PK parameters displayed a higher degree of normalization, and localized the malignant lesions better with reduced false positives. Further, this faciliated population studies as was indicated by the estimated ROC curves, which indicated that the M-S model yielded better discrimination between malignant and benign lesions than the Tofts model using the standard AIF.

2.3 Disadvantages of Pharmacokinetic analysis using the M-S model

The performance of the M-S model in population studies is tied to how reliably the reference region is selected across different datasets. It was first attempted to assign a form of reliability score to the choice of reference region to make it more robust. For example, if the reference region was set to be the nipple region for a set of analyses, the score would quantify with what probability the chosen reference region was the nipple region in that data set. However, given the extent of variablity in the sizes, shapes and intensity distributions of these anatomical structures across data sets, this score was not simple to formulate. The alternative is to eliminate the dependency of the performance on the choice of reference region and this forms the basis for the current work.

3 Proposed framework for Tofts model parameter estimation

The parameters of the M-S model are functions of the Tofts model parameters for the two voxels used - the voxel under analysis and the reference voxel. Ideally, the Tofts model parameters describe the concentration perfectly and can be assumed to be free of bias in the ideal situation where the exact AIF is known, and the estimation procedure yields zero error. The M-S model parameters are functions of these ideal Tofts model parameters. Hence, irrespective of the choice of reference region, if we could invert the model equations so as to estimate the Tofts model parameters from those of the M-S model, since all quantities used are from the available dataset, with ideal error-free estimation, the obtained values will be the exact Tofts model parameters. Additionally, these now describe the voxel concentration absolutely and hence the dependence on the choice of reference region has been eliminated, while retaining the advantage of not having to estimate the AIF to obtain the Tofts model parameters.
The primary issue in estimating the Tofts model parameters through the M-S model is that the latter only yields five parameters while in all, there are six values to be estimated (three each per voxel) for the extended Tofts model. This implies the need to introduce some form of redundancy (possibly by using multiple voxels), or to use some additional data.

3.1 Mathematical methodology

The M-S model parameters are related to the parameters of the Tofts model at the voxel under analysis and the reference voxel as shown by Equation 4.
We can solve these equations to obtain expressions for the various individuals Tofts model parameters. This simplification yields the following expressions:

$$\begin{aligned} v_p &= A_3 {v_p}^R \\ k^{trans} &= A_2 \frac{B_1 - B_2}{k_{ep}^R - B_2} v_p^R \\ k_{ep} &= B_2 \\ {k^{trans}}^R &= (B_1 - k_{ep}^R) v_p^R \end{aligned} \tag{5}$$

$$A_3 {k_{ep}^R}^2 - k_{ep}^R (A_1 + A_2 + A_3 B_1 + A_3 B_2) + (A_1 B_2 + A_2 B_1 + A_3 B_1 B_2) = 0 \tag{6}$$

Solving the quadratic equation 6 for k_{ep}^R, we get the following expression:

$$k_{ep}^R = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \tag{7}$$
$$a = A_3 \ , \ b = A_1 + A_2 + A_3 B_1 + A_3 B_2 \ \text{ and } \ c = A_1 B_2 + A_2 B_1 + A_3 B_1 B_2$$

These equations show that taking an inverse of the M-S model yields a quadratic equation and hence two possible solutions for k_{ep}^R. Also, the other quantities can be simplified to ratios with respect to ${v_p}^R$. This is the highest degree of

simplification possible for this system of equations. The quantities $\frac{k^{trans}}{v_p}$ and k_{ep} (which can both be determined) are in fact physically significant, however since our goal is to completely estimate the Tofts model parameters, we still face the challenge of determining ${v_p}^R$. This is discussed in the subsequent section.

3.2 Challenges in estimating Tofts model parameters

The quantities v_p (or v_p^R) and k^{trans} (or ${k^{trans}}^R$) both multiply terms containing the AIF in the Tofts model expression. Thus, even with the use of the above expressions, we can only estimate the quantities of interest as related to v_p^R. Since the AIF itself is also unknown at this point, this leaves us with two unknowns in the Tofts model expression. Separating out these two quantities is mathematically intractable, even with techniques like blind deconvolution.

3.3 Framework

The framework is made complete by the fact that the dosage of CA injected into each patient is known information. By understanding that the AIF is the concentration of CA fed into the tissue of interest, the implication is that the maximum value that the AIF can take is the injected dosage density itself. We can use this observation to compute v_p^R and thus all Tofts model parameters for all the voxels under analysis.

We start from the expression for the CA concentration at the reference voxel, by rewriting it as:

$$c_R(t) = v_p^R c_p(t) * (\delta(t) + \frac{{k^{trans}}^R}{v_p^R} e^{-k_{ep}^R t}) \tag{8}$$

Since the quantities k_{ep}^R and $\frac{{k^{trans}}^R}{v_p^R}$ are known, it is possible to use deconvolution to estimate $s(t) = v_p^R c_p(t)$. This expression was derived to be the following:

$$s(t) = v_p^R c_p(t) = c_R(t) - k_R e^{(k_R - k_{ep}^R)t} * c_R(t) \tag{9}$$

$$k_R = \frac{{k^{trans}}^R}{v_p^R} \tag{10}$$

The theoretical maximum of this signal is $v_p^R D$ where D is the dosage density of CA injected into the patient. Thus, to estimate the Tofts model parameters using Equation 5, we estimate v_p^R as:

$$v_p^R = \frac{max_t(s(t))}{D} \tag{11}$$

3.4 Implementation

The implementation of the proposed scheme is two-tiered. The first stage is the estimation of the M-S model parameters, and the second is the application of the Equations 5 and 7, coupled with the estimation of v_p^R using Equation 11 to obtain the Tofts model parameters. The estimation of the M-S model is discussed in detail in (1). The second stage essentially involves implementing the Equations 5 and 7. However, there are some associated challenges in practice. The first challenge in the proposed framework is the estimation of k_{ep}^R from

the quadratic equation in 6. This is because the M-S model estimate in the first step is not completely error-free and hence even with the same reference voxel used throughout the analysis for a given image, the quadratic equations yielded by the different voxels are not identical. The authors explored multiple heuristic approaches to this issue. One approach that works well is to weight highest the k_{ep}^R values yielded at the voxel with the lowest estimation error. The second challenge in the framework is that the dosage of CA is required to estimate v_p^R. In practice, data sets are encountered where the dosage (per unit body weight) is not known accurately. To circumvent this issue, the maximum enhancement in a given image was used as being proportional to the CA dosage. This yielded satisfactory results in practice and the results in this paper are with this approach.

4 Experiments, Results and Discussion

The experiments in this work aimed at evaluating the performance of the proposed framework in differentiating malignant lesions from benign by visual inspection and in population studies. The proposed framework was applied to a population of breast DCE-MRI data from 40 patients. The results included are from the application of the framework to a subset of this data. Also included are ROC curves comparing the performance of three PK analysis setups which are Tofts model estimation using the standard AIF, the framework for M-S model estimation and Tofts model estimation using the framework proposed in this paper with restricted and unrestricted choice of RR, all compared against a manual segmentation of the ground truth of the lesion. The visualized results in Figure 1 and the ROC comparison in Figure 2 (obtained by QLDA classifers) indicate that the framework achieves more robust differentiation than direct Tofts estimation. The visual comparison with two different choices of RR proves the hypothesis that the framework is robust to RR selection. Also, as compared to direct Tofts estimation, the proposed framework leads to more spatially clustered results and less scattered false positives which is desirable especially for use by radiologists in initial analysis. It is important to note that the current implementation uses an average value of dosage used per subject since the absolute values of dosage are known but the individual subject body weights are not known. This is also the same value of dosage as used in the standard AIF expression. Hence introducing the knowledge of body weights and thus average dosage per unit of body weight is expected to further improve the classification accuracy. Also, on closely studying the M-S model parameters estimated for each choice of RR, it becomes clear that the error in estimation of the M-S model - which propagates to the final Tofts estimate - is significantly different in the two cases. This brings into analysis the estimation procedure used - currently the conjugate gradient method - and the inference is that an alternate choice for the optimization method that yielded lower error on average, coupled with an unrestricted choice of RR, would result in improved clasification performance.

5 Conclusions and future work

The proposed framework for Tofts model parameter estimation using the M-S model, has been implemented and tested successfully on a population of breast

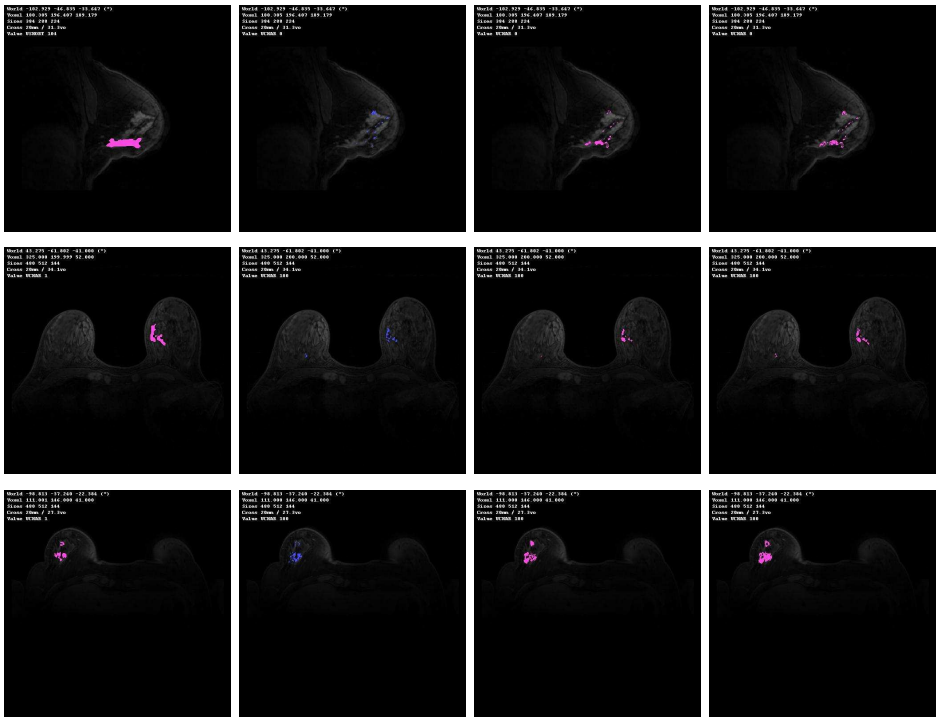

Fig. 1. Results comparing the manually segmented ground truth (Column 1) with results from direct Tofts Model estimation(Column 2); and the Proposed framework with restricted RR (Column 3) and unrestricted RR (Column 4). Note the improved localization of regions of interest, the reduction in false positives, and the improvement in results afforded by relaxing the restrictions on the RR.

DCE-MRI data from 40 subjects. The physical significance of the estimated parameters is well documented (2). As compared to direct estimation, the proposed framework does not use a standard AIF for all subjects and hence displays higher classification accuracy. The visualization shows that the estimated parameters display greater spatial clustering and accuracy than direct Tofts estimation. Further, it is demonstrated that these estimated parameters are indeed robust to the selection of reference region. The authors also identified areas of the framework with scope for improving system performance. These are the numerical optimization method for solving the M-S model, and the quantity used for the dosage per subject. These are being explored in future work for improving the framework accuracy in population studies.

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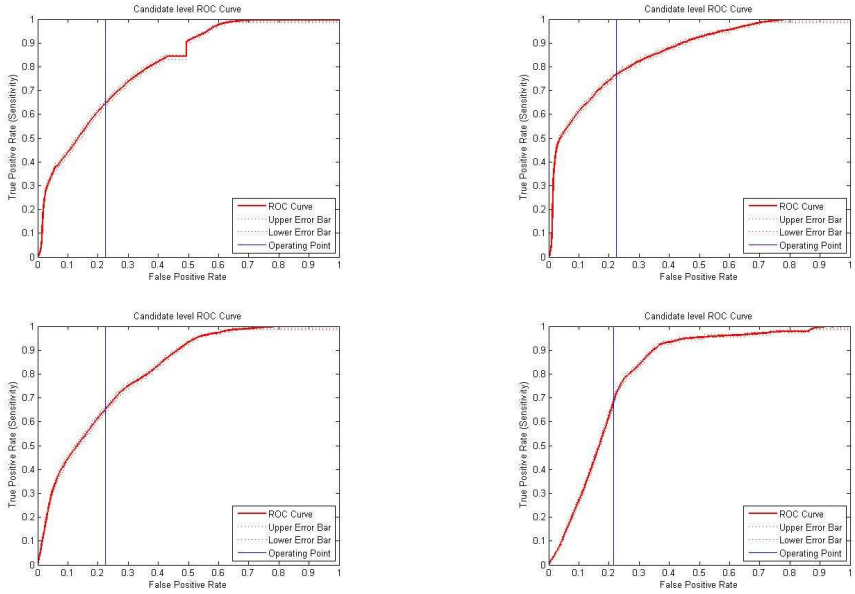

Fig. 2. ROC curves comparing the classification performance of PK analysis using (from L-R,Top-Bottom) direct Tofts' estimation, M-S model, proposed framework with restricted RR (nipple) and proposed framework with unrestricted RR

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